FAQ for Select Agent Regulation (42 CFR 73)

General Questions Concerning Select Biological and Toxins

1. What is the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and how do I find a copy?

On June 12, 2002, President Bush signed the "Public Health Security and Bioterrorism Preparedness Response Act of 2002" (Public Law 107-188). The law is designed to improve the ability of the United States to prevent, prepare for, and respond to bioterrorism and other public health emergencies. Section 202(a) of the Law requires that all persons possessing biological agents or toxins deemed a threat to public health to notify the Secretary, Department of Health and Human Services (HHS). Section 213(b) of Law requires all persons possessing biological agents or toxins deemed a threat to animal or plant health and to animal or plant products notify the Secretary, United States Department of Agriculture (USDA).

The Law also requires that both Secretaries be notified when a person possesses agents that appear on both the HHS and the USDA list of agents and toxins. These agents and toxins have been designated HHS/USDA overlap agents.

The Centers for Disease Control and Prevention (CDC) has been designated as the HHS agency responsible for providing guidance on this notification. The Animal and Plant Health Inspection Service (APHIS) has been designated as the USDA agency responsible for providing guidance on this notification.

For more information on the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107-188) see: http://www.cdc.gov/od/sap/addres.htm.

Subsequent to the enactment of Public Law 107-188, requirements for facilities or entities that possess, use, or transfer select agents and toxins have been published by HHS (42 CFR 73; December 13, 2002) and by USDA (9 CFR 121 and 7 CFR 331; December 13, 2002).

2. What is the USA PATRIOT Act and how does it relate to the select agent regulation? Where can I find a copy?

The USA PATRIOT Act is a law signed by President Bush on October 26, 2001, that places restrictions on persons who possess select agents and provides criminal penalties for possession of such agents that cannot be justified for specified peaceful purposes. More information on the PATRIOT Act can be found at: http://www.cdc.gov/od/sap/addres.htm.

3. What is a select agent or toxin ("select agent")? What is a High Consequence Pathogen and Toxin? How do they differ?

The original list of select agents was published in Appendix A of 42 CFR Part 72.6 ("Additional Requirements for Facilities Transferring or Receiving Select Agents," October 24, 1996). The list included approximately 40 viruses, bacteria, rickettsiae, fungi, and toxins that CDC considers to have potential to pose substantial harm to human health. The list of select agents in 42 CFR 72.6 is available at: http://www.cdc.gov/od/sap/42cfr72.htm. Under that regulation, laboratories were to register with CDC prior to transfer of select agents. The regulation and additional information may be found at: http://www.cdc.gov/od/sap/42cfr72.htm.

A listing of HHS select agents and toxins in the select agent regulation (42 CFR 73) is available at http://www.cdc.gov/od/sap.

High Consequence Livestock Pathogens and Toxins are agents that the USDA considers to have the potential to pose a severe threat to animal or plant health, or to animal or plant products. A list of the agents may be found at: http://www.aphis.usda.gov/vs/ncie/bta.html.

Agents that appear on both the HHS and USDA list of agents and toxins are referred to as "Overlap Agents." The list of overlap agents is available at: http://www.cdc.gov/od/sap or http://www.aphis.usda.gov/vs/ncie.

The plant pathogens listed by USDA have been deemed a threat to plant health or products. The list of plant agents and toxins is available at http://www.aphis.usda.gov/ppq/permits.

4. Why do I need to register with HHS and USDA for select agents that I may possess or use?

Agents identified under the HHS and USDA lists of biological select agents and toxins or USDA's list of High Consequence Livestock Pathogens and Toxins have been deemed a potential threat to human, animal, or plant health or animal or plant products. The registration of facilities possessing and using these agents or toxins is part of the government's efforts to improve the ability of the United States to prevent, prepare for, and respond to bioterrorism and other public health emergencies and is required under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.

Reporting Possession of Select Agents

1. What is the difference between notification and registration?

Under the new Public Health Security and Bioterrorism Preparedness Act, all facilities that possessed an HHS select agent or toxin, or a USDA "High Consequence Livestock Pathogens and Toxins" were required to notify HHS by September 10, 2002 and/or USDA by October 11, 2002. This was a one-time notification process. The specific requirements for reporting were published in a Federal Register Notice on July 12, 2002. **The notification period has passed**.

The current registration process requires submission of an application that certifies that the facility is in compliance with specific safety and security standards set forth in the regulation. More information is available at http://www.cdc.gov/od/sap.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002, required both HHS and USDA to publish an interim final rule in the Federal Register that will describe the regulations and registration processes for both agencies.

2. Can I still notify HHS and USDA that I possess select agents?

If you have questions or concerns regarding this activity, please call 404-498-2250.

General Questions Regarding the Select Agent Regulation (42 CFR 73)

1. Where can I find a copy of the interim final rule?

The regulation published by HHS concerning HHS and HHS/USDA overlap select agents and toxins (42 CFR 73, December 13, 2002) is available at: http://www.cdc.gov/od/sap. The regulations published by CDC/APHIS for HHS/USDA overlap and USDA high consequence livestock and pathogens and for listed plant agents (9 CFR 121 and 7 CFR 331, December 13, 2002) are available at: http://www.aphis.usda.gov/.

2. How was the select agent list determined?

CDC prepared the select agent list for 42 CFR 73 after receiving extensive input from scientists representing 21 Federal government entities. The proposed list was published in the Federal Register for public comment on August 23, 2002.

The HHS Secretary considered the following criteria for establishing the list as directed in 42 U.S.C. 262a (a)(1)(B):

- The effect on human health of exposure to the agent or toxin;
- The degree of contagiousness of the agent or potency of the toxin and the methods by which the agent or toxin is transferred to humans;
- The availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin.

3. What is an entity?

An entity is any government agency (Federal, State, or local), academic institution, corporation, company, partnership, society, association, firm, sole proprietorship, or other legal entity.

4. What changes will affect CLIA labs? Does 42 CFR 73.6(a)(1) automatically include and replace the previous CLIA exemption?

Any diagnostic or CLIA lab that does diagnostic testing, verification or proficiency testing is exempt from the regulation. The laboratory director must notify HHS immediately upon identifying specific select agents; the entity must transfer the agents to a registered facility or destroy them (unless directed otherwise by law enforcement or HHS) within 7 calendar days of identification of the select agent. See number 7 and 8, below. NOTE: Retention of any select agent as a positive control or reference sample is no longer exempt for any reason.

5. Who is exempt from the 42 CFR 73 ?

An entity may be exempt from the provisions of the regulation, if:

- The only activities that an entity conducts concerning select agents are processing diagnostic, verification or proficiency specimens or isolates (see § 73.6 for details on additional requirements for these laboratories. Also see number 8, below).
- The entity has select agents or toxins that are cleared, approved, licensed, or registered under any of the laws specified in the regulation, and are used only for the approved purpose of such laws.
- The entity applies to CDC and/or APHIS as appropriate for an exemption for select agents or toxins that are an investigational product authorized under a Federal Act listed in the regulation. CDC form 0.1317/APHIS form 2042. http://www.cdc.gov/od/sap/forms/exempts.pdf
- An exemption is granted by CDC and/or APHIS due to a public health or agricultural emergency.

6. Our entity has been exempt since we are a diagnostic/clinical laboratory. What are we required to do under 42 CFR 73?

- Even if exempt, the entity must immediately report to CDC (telephone: 404-498-2255, facsimile: 404-498-2265, or to lrsat@cdc.gov) the identification of the following select agents: Variola major virus (Smallpox virus) and Variola minor (Alastrim), *Bacillus anthracis*, *Yersinia pestis*, Botulinum neurotoxins, *Francisella tularensis*, Ebola viruses, Marburg virus, Lassa fever virus, and South American Haemorrhagic Fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito).
- The entity reports as required under Federal, State, or local law, to appropriate authorities.
- After diagnosis, verification or proficiency testing, the entity either transfers the specimens or isolates to a registered facility or destroys them on-site by an appropriate method.
- Select agents used for diagnosis or verification testing are transferred or destroyed within 7 days after identification, unless directed otherwise by the FBI or other law enforcement agency after consultation with the HHS Secretary.
- Select agents used for proficiency testing are transferred or destroyed within 90 days after receipt.
- The entity makes a written record of the identification and transfer or destruction on CDC Form 0.1318, submits the form to the HHS Secretary (within 7 days after identification or 90 days after receipt for proficiency testing).
- The entity maintains a copy of the record for a period of three years.

7. Under what conditions is an entity excluded from the select agent regulation (42 CFR 73)?

The following are excluded from the regulation:

- Select agents or toxins that are in their naturally occurring environment, provided that it has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.
- Non-viable select agent organisms or nonfunctional toxins.
- The vaccine strain of Junin virus (Candid #1).
- It is possible under the rule to apply for exclusion for any attenuated agent or toxin using an appropriate form obtainable from CDC. Exclusions for specific strains may be granted if the attenuated strain is determined not to pose a significant public health or safety threat. Exclusions for specific strains should be requested in writing and sent to the Select Agent Program. Exclusions will be published in the notice section of the Federal Register and will be listed on the CDC website at http://www.cdc.gov/od/sap/exclusion.htm
- Exclusions for entities with specific quantities of toxins under the control of a principal investigator at a given time are also detailed in the regulation (see number 10, below).

8. What specific changes in the list of agents take effect in the regulation when compared to the agents and toxins listed in 42 CFR 72.6? (For USDA only agents see: http://www.aphis.usda.gov/vs/ncie.)

- Two agents (viruses causing Hantavirus pulmonary syndrome and yellow fever virus) have been removed from the list. One toxin (aflatoxin) was removed from the list previously published in 42 CFR 72.6.
- Several agents have been added to the list of HHS agents, including Cercopithecine herpes virus 1 (Herpes B virus), Monkeypox virus, *Coccidioides posadasii*, and Shiga-like ribosome inactivating proteins.
- Nomenclature changes are as follows:
  Equine Morbillivirus Virus has been renamed to Nipah and Hendra Complex viruses; *Clostridium botulinum* was updated to include botulinum neurotoxin producing species of *Clostridium*. Tick borne encephalitis complex (flavi) viruses are now specified by individual name (Central European Tick-Borne encephalitis (CTBE); Far Eastern Tick-borne encephalitis (including Russian Spring and Summer encephalitis (RSSE), Kyasanur Forest disease, and Omsk hemorrhagic fever). The listing of Variola minor virus (Alastrim) is added to Variola major (smallpox) virus.

Toxins are regulated based on potency and quantity (as opposed to potency only or LD50 values as in 42 CFR 72.6). If the aggregate amount under the control of a principal investigator does not at any time exceed the amount specified in the regulation, the toxins are not subject to the regulation. For a list of permissible amounts per principal investigator, please see http://www.cdc.gov/od/sap/toxinamt.htm.

9. Who must register?

Any entity that possesses, uses, or will receive or transfer any select agent or toxin to or from entities within the US or outside the US are subject to 42 CFR 73.

10. Where can I obtain an application?

The application is available at http://www.cdc.gov/od/sap/downloads2.htm. We now have the application in a PDF fillable format as well as Excel templates of the tables contained in the application. You may also directly contact our office via phone at 404-498-2255 or facsimile 404-498-2265 to obtain an application package.

11. What are the duties of the Responsible Official (RO)?

The RO is responsible for ensuring compliance with the regulations including:

- Developing and implementing safety, security and emergency response plans;
- Allowing only approved individuals to have access to select agents or toxins.
- Providing appropriate training for safety, security, and emergency response.
- Transferring select agents or toxins.
- Providing timely notice of any theft, loss or release of a select agent or toxin.
- Maintaining detailed records of information necessary to give a complete accounting of all activities related to select agents or toxins.
- Reporting the identification of a select agent or toxin as a result of diagnosis, verification or proficiency testing.

CDC recommends that the RO and alternate RO are biosafety officers or senior management officials of the entity/facility, or both. Although we understand that some entities have limited staff, we recommend that the RO not be an individual actually using, working with, or transferring or receiving the select agents and toxins to minimize potential conflicts of interest.

12. What is the responsibility of the alternate RO?

The alternate RO must meet all the qualifications for the RO and must be able to conduct all the activities of the RO (listed above) in the absence of the RO.

13. What agency should the application be submitted to?

The agency that the Responsible Official (RO) should contact is determined by the type of select biological agent or toxin that is possessed.

- For HHS agents, the RO should contact CDC (telephone: 404-498-2255; facsimile 404-498-2265).

- For USDA agents (animal agents and toxins), the RO should contact APHIS (telephone: 301-734-3277; facsimile: 301-734-3652).
- For HHS/USDA overlap agents, the RO may contact either APHIS or the CDC.
- For plant agents and toxins the RO should contact APHIS (telephone: 301-734-5519; facsimile: 301-734-8700).
- A listing of HHS and USDA select biological agents and toxins is available at http://www.cdc.gov/od/sap/docs/salist.pdf

14. Will one or both agencies approve applications that include overlap select agents?

Regardless of which agency receives the application regarding an overlap select agent or toxin, both agencies will provide input before a determination is made to grant or deny a certificate of registration.

15. What does the registration cover?

The registration will only be valid for the specific select agents and toxins and the specific activities and locations consistent with the information which the certificate of registration or amendment is granted.

16. What if we need to update, change, or amend our registration?

If any change occurs in the information submitted, the Responsible Official (RO) of the entity must obtain prior approval by promptly notifying the CDC in writing in accordance with 42 CFR 73.21. This includes modifications to the list of individuals that have been approved under 42 CFR 73.8 to work/access select agents, changes in work locations, and changes in protocols or objectives of the studies. The entity must submit the information requested in the relevant portion of the application package to the agency that issued the certificate of registration.

17. Under what conditions could a registration be terminated?

The HHS Secretary will terminate a certificate of registration based on a determination that the entity no longer conducts activities covered by the certificate. It may also be terminated based on the security risk assessment from Department of Justice, or if the entity fails to meet or maintain safety or security requirements as specified in 42 CFR 73. The HHS Secretary may take such action immediately if necessary to protect the public health or safety. Upon such termination the select agent or toxin possessed by the entity must be destroyed or transferred as directed by the HHS Secretary.

18. Who has to have a security risk assessment?

All entities (except for Federal, State, or local governmental agencies), the RO, alternate RO, and all individuals with access to select agents or toxins must have an approved

security risk assessment. Please see our website http://www.cdc.gov/od/sap/securisk.htm or the FBI website http://www.fbi.gov/terrorinfo/bioterrorfd961.htm for additional information.

19. Please provide us with additional guidance on security risk assessments and security requirements.

Section 73.8(b)(Security risk assessments) states that an entity may not provide an individual access to a select agent or toxin unless the individual has been approved by the Secretary of either HHS or USDA, based on a security risk assessment conducted by the Attorney General. "Access" as it is used in these regulations takes its ordinary meaning: "the freedom or ability to obtain or make use of." Anyone, including visitors, who have the freedom or ability to obtain and make use of a select agent or toxin, must be approved. Also see section 73.11(d)(1) (Security). However, the regulations do recognize that access to a select agent or toxin can, as a practical matter, be limited by either security containers or by escorts. As provided in 73.11(d)(2) regarding non-laboratory functions including routine cleaning, maintenance, and repairs, non-approved individuals will be allowed access to areas where select agents are accessible only if they are escorted and monitored by an individual who has been approved. It is the intent of the regulations that the escort will have the means and ability to prevent the non-approved individual from obtaining or making use of any accessible select agent or toxin in that area.

With regard to record keeping, Section 73.15(a) requires that an entity keep an up-to-date list of everyone who has been approved for access to select agents and toxins. Section 73.15(c)(1) requires that an entity must maintain a record of each individual who has actually accessed a select agent or toxin. Section 73.15(c)(2) requires that an entity must maintain a record of each individual who has actually accessed any area where select agents are used or stored. Depending on the circumstances, maintenance of some of the records may be manual or electronic (e.g., electronic key cards that records access to labs). The record may consist of one list or three, but each section of the regulations requires the entry of specific information. For example: For a researcher working directly with a select agent or toxin, the record must show the name of the researcher; the name of agent or toxin; if long-term storage or holding was involved, the dates of removal and returns; and, if a toxin, the quantity removed and returned. Another example: For a maintenance person doing routine cleaning of an area (i.e., a lab) in which a select agent or toxin was stored (even locked storage), the record must show the name of the person who had entered the area, the date and time the person entered and left; and, if escort is required, the name of the escort.

20. What is the general process for obtaining a security risk assessment (SRA)?

The following process applies to a new application or an amendment to an existing application.

- The entity Responsible Official (RO) submits an application or amendment that includes a Table 4B (CDC Form 0.1319/USDA Form 2044) to their lead agency (APHIS or CDC, but not both). The lead agency serves as single point of contact for an entity and is responsible for coordinating all activities and communications with respect to new applications or amendments;
- The lead agency issues back to the entity a letter with the unique Department of Justice (DOJ) identifying number for each individual listed on the Table 4B or amended 4B;
- The RO forwards to each individual their unique DOJ identifying number;
- The individual fills out FBI form (FD-961) and puts their unique identifying number in block 15;
- The individual follows all of the FBI instructions (http://www.fbi.gov/hq/cjisd/takingfps.html) for submitting fingerprints; and
- The individual mails the FD-961 form and fingerprint cards *as one package* directly to the FBI, Criminal Justice Information Services Division (CJIS), not to APHIS or CDC.

  FBI, CJIS, Bioterrorism
  1000 Custer Hollow Road, Module E-3
  Clarksburg, WV 26306-0147

Please see our website http://www.cdc.gov/od/sap/securisk.htm or the FBI website http://www.fbi.gov/terrorinfo/bioterrorfd961.htm for additional information.

NOTE: All FBI FD-961 forms received by APHIS or CDC will be returned directly to the RO of the entity which will delay the processing of SRAs.

21. What is the procedure if an individual from one registered entity wants to visit another registered entity?

- If the individual(s) will have access to select agents or toxins, the receiving entity RO should request the sending entity RO to provide a letter stating that the individual(s) is currently identified on Table 4B of the sending entity's registration. The receiving entity is defined as the entity where the training, work or visit will take place. The sending entity is defined as the entity where the individual(s) are currently located. The individual must have a current SRA approval. The letter should include: individual's full name, date of birth, date of issuance of the SRA approval and unique DOJ identifying number of the individual(s).
- The receiving entity RO should submit this letter and an amendment to the registration to the lead agency (APHIS or CDC). The amendment should provide updated Tables 4A and 4B, and Sections 5B through 5G, where applicable (e.g., Principal Investigator, specific agents or toxins, specific laboratory buildings/rooms, etc.).

- Once the visit is complete, the receiving entity RO should amend the entity's registration to remove the visiting individual's name from the Table 4B. In some circumstances the receiving entity RO may decide to leave the individual(s) on the registration, if the same individual(s) will be visiting the entity again.

22. What is the procedure if an individual from an unregistered entity wants to visit a registered entity?

- If an individual(s) will have access to select agents or toxins, they must have a current security risk assessment. Follow the procedures as indicated in Question 1, above.
- Once the visit is complete, the receiving entity RO should amend the entity's registration to remove the visiting individual's name from the Table 4B. In some circumstances the receiving entity RO may decide to leave the individual(s) on the registration, if the same individual(s) will be visiting the entity again.

If you have questions regarding completion of the FD-961 form, contact the FBI directly at (304) 625-4900 or visit http://www.fbi.gov/terrorinfo/bioterrorfd961.htm. Written requests may be faxed to (304) 625-5393 (for FD-961 forms) or (304) 625-3984 *(*for fingerprint cards). These faxed requests should include the following: entity name, point of contact or RO, mailing address, contact telephone number and the number of fingerprint card packets requested.

If you have questions concerning the FBI/CJIS SRA process, contact FBI/CJIS at (304) 625-4900. If you have questions on how to obtain a DOJ unique identifying number, contact your lead agency (CDC: (404) 498-2255; or USDA: (301) 734-5960).

23. What criteria are used for determining approval of a security risk assessment?

The security risk assessment will evaluate if an individual is a restricted person based on the criteria of the PATRIOT Act http://www.cdc.gov/od/sap/addres.htm, has committed a Federal crime, is involved with any group that engages in domestic or international terrorism or any organization that engages in intentional acts of violence, or is an agent of a foreign power.

24. How long is the security risk assessment valid?

It is valid for a period of five years unless terminated by the HHS Secretary sooner.

25. What are the safety requirements of the select agent regulation?

Each entity must implement a safety plan. This safety plan should consider:

- The requirements of the Biosafety in Microbiological and Biomedical Laboratories (BMBL), including all appendices except Appendix F.

- The requirements for handling toxins found in the 29 CFR 1910.1450 and / or 29 CFR 1910.1200, and Appendix I of the BMBL.
- NIH Guidelines for Research Involving Recombinant DNA (NIH Guidelines) for work with genetic elements, recombinant nucleic acids, and recombinant organisms.

26. What are the responsibilities of the RO with respect to the safety requirement?

The RO must conduct regular inspections, at least annually, of the laboratory where select agents or toxins are stored or used to ensure compliance with all procedures and protocols of the safety plan. The results of these inspections must be documented and any deficiencies must be corrected.

27. What other safety requirements are included in the regulation?

An entity may not conduct the following types of experiments unless approved by the HHS Secretary:

- Utilizing recombinant DNA to deliberately transfer drug resistance traits to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the use of drug to control disease agents in humans, veterinary medicine, or agriculture.
- Work involving the deliberate formation of recombinant DNA containing genes for the synthesis of select agent toxins lethal for vertebrates at an $LD_{50} < 100$ ng/kg body weight.

28. What are the requirements of the security plan?

The specific components to include in the security plan as required by 42 CFR 73 are located in part § 73.11 of the regulation. http://www.cdc.gov/od/sap/docs/42cfr73.pdf

29. What records are entities required to keep and for what duration?

Records that should be kept include: the list of approved individuals that may access select agents, inventories, access to agents and toxins, areas where agents are used, and transfer and destruction documents. These should be maintained for a period of three years, as described in 42 CFR 73 part § 73.15.
http://www.cdc.gov/od/sap/docs/42cfr73.pdf

30. When and how will inspections take place?

Inspectors from the CDC Select Agent Program will conduct inspections of registered entities. Such inspections may be conducted without prior notification and will include a

review of all safety and security aspects, as well as record keeping requirements, covered by 42 CFR Part 73.

31. Are there criminal or civil penalties for not being in compliance with the regulation? If yes, what are they?

Violation of the Public Health Security and Bioterrorism Preparedness Response Act of 2002 can result in substantial fines or imprisonment of up to 5 years, or both. In addition, violation of the Law can result in a civil money penalty of up to $250,000 for individuals and $500,000 for an entity.

32. Please provide us with additional guidance regarding genomic material from select agents that is subject to 42 CFR 73.

The following is from 42 CFR 73.4(e) and 73.5(e) and specifies genetic elements, recombinant nucleic acids, and recombinant organisms that are subject to the requirements of 42 CFR Part 73 (Possession, Use, and Transfer of Select Agents and Toxins):

1. Select agent viral nucleic acids (synthetic or naturally derived, contiguous or fragmented, in host chromosomes or in expression vectors) that can encode infectious and/or replication competent forms of any of the select agent viruses.
2. Nucleic acids (synthetic or naturally derived) that encode for the functional form(s) of any of the toxins listed in paragraph (d) of this section if the nucleic acids:
    i. Are in a vector or host chromosome; or
    ii. Can be expressed in vivo or in vitro; or
    iii. Are in a vector or host chromosome and can be expressed in vivo or in vitro.
3. Viruses, bacteria, fungi, and toxins listed in paragraphs (a) through (d) of this section that have been genetically modified.

Additional clarification:

- Non-viable select agent organisms (including agents in fixed tissues). Select agent organisms that have been treated in such a manner (e.g., gamma irradiation) that they are no longer able to replicate (i.e. non-viable, inactivated, killed, or dead) are not select agents. See 42 Parts 73.4(f)(2) and 73.5 (f)(2).
- Purified genomic material or genetic elements from select agent viruses Genetic elements (nucleic acids) from select agent viruses are regulated if in host chromosomes or expression vectors and if it encodes for infectious or replication competent forms of any of the select agent viruses. See 42 Parts 73.4(e)(1) and 73.5 (e)(1).
- Purified genomic material or genetic elements from select agent bacteria are select agents if the nucleic acid encodes for a functional form of a listed toxin in a

vector or host chromosome and/or can be expressed in vivo or in vitro. See 42 Parts 73.4(e)(2) and 73.5 (e)(2).

Note that the HHS select agents and toxins are listed in 42 CFR Parts 73.4 (a-e) and overlap select agents and toxins are listed in (42 CFR Parts 73.5 (a-e)). It is the responsibility of the entity (specifically the Responsible Official) to ascertain if you must register under 42 CFR 73.

33. Do laboratories working with organisms that are not on the select agent list (e.g., Shigella dysenteriae, Escherichia coli, Staphylococcus aureus, etc.) that produce select agent toxins have to register under 42 C.F.R. Part 73?

Only the organisms listed in 42 C.F.R. sections 73.4 and 73.5 are subject to the requirements of 42 C.F.R. Part 73. However, if the organism produces a listed toxin, then the toxin will be subject to the requirements of 42 C.F.R. Part 73 if the aggregate amount exceeds that specified in 73.4 or 73.5.

34. Do laboratories working with recombinant DNA or genomic material from organisms that produce select agent toxins have to register under 42 C.F.R. Part 73?

Genetic elements from organisms that produce listed toxins are select agents if the nucleic acid encodes for a functional form of a listed toxin in a vector or host chromosome and/or can be expressed in vivo or in vitro. See 42 Parts 73.4(e)(2) and 73.5 (e)(2).

35. Are attenuated strains excluded from the regulation?

Attenuated strains of select agent organisms excluded from 42 CFR 73 are Junin Virus (Candid #1), Rift Valley fever virus (MP-12), and Venezuelan Equine encephalitis virus vaccine strain TC-83. Exclusion of additional strains of select agents will be evaluated at the request of individuals and entities. To apply for an exclusion, an applicant must submit a letter to the HHS Secretary (see 42 CFR 73.21) or to the USDA Secretary (9 CFR 121 that provides information that establishes that it is eligible for exclusion. Information should include at a minimum: strain, how strain was derived; how it is ascertained that it is avirulent, and all citation or pertinent data to support your request.

In response to the request for exclusion, the HHS Secretary or the USDA Secretary (or both, for overlap agents) will provide a written decision granting the request in whole or in part or denying the request. Exclusions will be published in the Federal Register, and are posted on the CDC internet site (http://www.cdc.gov/od/sap/). An exclusion will be effective upon notification to the applicant. Until such time that exclusions are considered and granted, entities must apply for registration of the select agent. Requests for review of an attenuated strain of an HHS agent should be mailed to:

Select Agent Program
Centers for Disease Control and Prevention
1600 Clifton Road, NE, Mail Stop E 79
Atlanta, GA 30333
FAX (404) 498–2265

For overlap agents, a request for review should be mailed to CDC (above address) or to:

National Center for Import and Export, VS
APHIS
4700 River Road Unit 40
Riverdale, MD 20737–1231
FAX (301) 734–3652

36. What is the difference between an "exemption" and "exclusion" in the context of 42 C.F.R. Part 73?

The "exclusions" found in 42 C.F.R. 73.4(f) and 42 C.F.R. 73.5(f) apply to only to those biological agents and toxins designated in 42 C.F.R. 73.4 and 42 C.F.R. 73.5 as "HHS select agents and toxins" and "Overlap select agents and toxins," respectively. The practical effect is to exclude, in the circumstances and conditions specified in the regulation, a biological agent or toxin that has otherwise been listed as a select agent or toxin from the provisions of the regulations. The "exclusions" set out in 42 C.F.R. 73.4(f)(1)-(4) and 42 C.F.R. 73.5(f)(1)-(4) are automatic. In addition, subsection (f)(5) of each section provides that, upon request, the Secretary may exclude attenuated strains of select agents or toxins upon a determination by the Secretary that they do not pose a severe threat to the public health and safety.

The "Exemptions" found in 42 C.F.R. 73.6 were mandated by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. They list five different categories under which an entity; biological agent or toxin, or individual may be permanently or temporarily exempted from some or all of the provisions of Part 73 depending of the specifics of a particular exemption.

37. Please provide us with additional guidance on 42 C.F.R. 73.11(d)(4) which states "Require the inspection of all packages upon entry and exit from the area."

The term "package" as used in the regulation (42 C.F.R. 73.11(d)(4)) takes its ordinary meaning: "a wrapped or boxed object, parcel, or container in which something is packed."

All unexpected or suspicious packages should be inspected by visual or noninvasive techniques before they are brought into, or removed from, the area where select agents or

toxins are used or stored. Guidelines for recognizing suspicious packages have been provided by the U.S. Postal Service and can be found at: http://www.usps.com/news/2001/press/pr01_1010tips.htm. If unexpected or suspicious packages are received, then the sender should be contacted to verify that the package is legitimate. If any individual observes suspicious packages being transported out of the laboratory (for example, packages that have an unusual weight or size), then they should immediately notify the appropriate authorities. Common sense should be employed in maintaining vigilance with respect to control of access to select agent(s) and toxin(s). This guidance is considered a minimum standard. After further evaluation, entities may choose to exercise greater control over materials entering and leaving their facilities.

38. What do entities that plan to conduct training at their facilities need to do in order to meet the requirements of 42 CFR 73?

First, the entity responsible for the training should determine if the agents or toxins they wish to use in the training meet the definition of a select agent or toxin as defined in 42 CFR 73.4, 42 CFR 73.5, and 7 CFR 331.3 (a). Please note that some exclusions have been specified in 42 CFR 72.4(f)(1-4) and 42 CFR 72.5(f)(1-4). In addition, some select agent strains have been excluded from the regulation. This list of excluded select agent strains is posted at: http://www.cdc.gov/od/sap/exclusion.htm. If the material (i.e., isolates or diagnostic/clinical samples) being used in the training event meets the exclusion criteria, then it is considered excluded from the regulation and therefore is not subject to the registration, transfer, record-keeping and other requirements of 42 CFR 73.

If the entity will be using select agents or toxins in their training event, then current information regarding the entity, the principal investigator (PI) responsible for the select agents or toxins used in the training, and the laboratory rooms used in the training, must be on file with CDC's Select Agent Program (or, in the case of overlap agents, with CDC or APHIS). If this information is not on file with the CDC Select Agent Program, then the entity should amend their application for registration with us. The Responsible Official (RO) should contact our office at 404-498-2255 if they have questions on how to amend their application for registration with us.

The Responsible Official (RO) from the entity will also need to submit the following information to the CDC Select Agent Program at least 8 weeks prior to the training event:

1. A summary of what type of training will occur, where it will occur and when it will occur. Include in your summary:
    a. Date of event,
    b. Building and laboratory room numbers where event will occur,
    c. Objectives of the training event (2-3 sentences)

2. An updated Table 4B that lists personnel with authorized access, their affiliations and the specific agents that they will have access to at the entity that is sponsoring the training. Before 11/11/03, these individuals must have filed the FBI security

risk assessment form (FD-961) and fingerprints prior to the event. On or after 11/12/03, these individuals will require approved security risk assessments from the FBI specific to the entity where training is conducted. See question 22 for additional details.

3. A statement as to whether the participants will handle select agents during the training event. If participants will have direct access to select agents or toxins during the training, then provide their names with number 2, above.

4. When the training event is over, the RO must provide CDC's Select Agent Program with an update to remove authorized personnel from the entity registration.

The entity should submit paperwork well in advance of the training event to ensure that a delay of the training will not occur. For additional clarification contact CDC's Select Agent Program by telephone (404-498-2255), facsimile (404-498-2265), e-mail (lrsat@cdc.gov), or mail at:

Centers for Disease Control and Prevention
Select Agent Program
1600 Clifton Rd NE, Mailstop E-79
Atlanta GA 30333

39. Do we need to register toxin subunits?

Sections 73.4(f) and 73.5(f) titled Exclusions, subsection (2) states: "This section does not include non-viable select agent organisms or nonfunctional toxins." Thus, if the entity determines that the toxin subunits are not functional toxins, then the material is considered excluded from the regulation and therefore not subject to the requirements of 42 C.F.R. Part 73, including the registration and transfer requirements. However, registration is required if the subunits are combined to become functional toxins and the aggregate amount of the functional toxin under the control of a principal investigator exceeds the amount specified by the regulation in sections 73.4(f)(4) or 73.5(f)(4).

Note that the HHS select agents and toxins are listed in 42 C.F.R. §§ 73.4(a)-(e) and overlap select agents and toxins are listed in 42 CFR §§ 73.5(a)-(e). It is the responsibility of the entity (specifically the Responsible Official) to ascertain if you must register under 42 C.F.R. Part 73.

40. Do we need to register if we are using plasmids to express toxin subunits?

The following is from 42 C.F.R. §§73.4(e) and 73.5(e), which specifies genetic elements, recombinant nucleic acids, and recombinant organisms that are subject to the requirements of 42 C.F.R. Part 73:

2. Nucleic acids (synthetic or naturally derived) that encode for the functional form(s) of any of the toxins listed in paragraph (d) of this section if the nucleic acids:
    i. Are in a vector or host chromosome; or
    ii. Can be expressed in vivo or in vitro; or
    iii. Are in a vector or host chromosome and can be expressed in vivo or in vitro.

3. Viruses, bacteria, fungi, and toxins listed in paragraphs (a) through (d) of this section that have been genetically modified.

If the entity determines that the clone is expressing a DNA sequence that does not encode for the functional form of any listed toxin, then the material is considered excluded from the regulation and therefore not subject to the requirements of 42 C.F.R. Part 73, including the registration and transfer requirements. However, if the DNA encodes for the functional form of a listed toxin (not a fragment of the toxin) and is in a vector or host chromosome and/or can be expressed in vivo or in vitro, then the material would be subject to regulation. (See 42 C.F.R. §73.5(e)(2)). It is the responsibility of the facility (specifically the Responsible Official) to ascertain if the facility should register under 42 C.F.R. Part 73.

41. Currently we only store select agents and toxins, do we have to register personnel with access to the freezers with DOJ?

Yes. You must submit application for a security risk assessment to DOJ for any individuals that require access, including the appointed RO and alternate RO.

42. I just received a letter with a response due date from the inspector assigned to my facility. Is there a process by which I can request to extend this response date?

The regulation specifically provides for an 8-week period of processing of the application. This time is to allow you to provide information that is required, but was not furnished with your application. As noted on the application, information not provided can seriously delay processing of your application, and may result in delaying your registration.

43. We are a facility that is currently registered with CDC to transfer select agents, but due to funding constraints for the select agent project, we are considering eliminating the project and destroying the agent. What should we do?

CDC must be notified in writing at least 5 business days prior to destruction (see 42 CFR 73.7(h)).

44. What are the requirements for importing select agents or toxins from countries outside the United States if I am registered with the CDC Select Agent Program?

In order for an entity to import select agents or toxins from outside the United States, the following is required:

1. The importer must hold a valid import permit from CDC in accordance with 42 CFR Part 71.54 (Importation of etiologic agents, hosts, and vectors). The application and instructions for obtaining import permits for etiologic agents is available through the CDC website at: http://www.cdc.gov/od/ohs/biosfty/imprtper.htm or by calling the CDC fax information service at 1-888-232-3299 and requesting document number 101000. Please note that additional permits may be required, such as those issued by the United States Department of Agriculture. Information on other permits that may be required can be found at: http://www.cdc.gov/od/ohs/biosfty/bmbl4/b4ac.htm.
2. The importer must be registered with the CDC Select Agent Program in accordance with 42 CFR Part 73 (Possession, Use, and Transfer of Select Agents and Toxins; Interim Final Rule) for the select agent listed on the import permit application. The CDC Select Agent Program application for registration is available through the CDC website at: http://www.cdc.gov/od/sap/downloads2.htm or by calling 404-498-2255.
3. In accordance with 42 CFR Part 73.14(a)(3), a CDC Form EA-101 must be completed and submitted to the CDC Select Agent Program. The CDC Select Agent Program must grant approval prior to the shipment of the select agents or toxins under the import permit. The CDC EA-101 form is available through the CDC website at: http://www.cdc.gov/od/sap/addforms.htm or by calling 404-498-2255.

   The receiving/recipient Responsible Official (RO) must complete CDC Form EA-101:
   A. Completes Blocks 1 and 2 as instructed.
   B. Completes Block 3 and 4 for sender, placing the "PHS Permit Number" in the Importation box.
   C. Faxes form EA-101 to CDC (Fax: 404-498-2265) for CDC confirmation number.
   D. The sender must comply with all applicable laws concerning importation, packaging, and shipping. Some additional permit and transportation regulations are found in Appendix C of the 4th edition of the CDC/NIH publication "Biosafety in Microbiological and Biomedical Laboratories" (http://www.cdc.gov/od/ohs/biosfty/biosfty.htm).
   E. After receipt of material, completes Block 4 with date the material was received and faxes completed EA-101 form to CDC within 2 days of receiving the select agent or toxin. If the select agent or toxin is not received within 48 hours of the expected delivery time or if the package containing select agent is leaking or otherwise damaged, then the receiver

of the material must immediately report this information to CDC (Tel: 404-498-2255).

F. Retains paper record for 3 years.

45. We have select agents on the exclusive HHS list as well as on the exclusive USDA list. Do we have to register with both HHS (CDC) and USDA (APHIS)?

No. In order to minimize the burden to the public that register for select agents and toxins, CDC and APHIS are working together to provide a single point of contact. This single point of contact is referred to as the lead agency, and as such, is responsible for coordinating all activities and communications with respect to your registration, including coordination with both the non-lead agency and with FBI/CJIS. The lead agency will retain responsibility for your application through the life of your registration certificate (2-3 years), even if your entity chooses to discontinue registration of overlap agents.

Please be advised that you have a choice in the agency you wish to manage your application for registration, and after you are registered, all activities associated with your registration.

- If your entity possesses overlap agents, the RO can file an application with either CDC or APHIS. For entities that have HHS and/or USDA agents in addition to overlap agents, they may file one application with either CDC or APHIS. This agency will be responsible for coordinating and obtaining concurrence with the non-lead agency, including those activities involving agents regulated by the non-lead agency.

- For agents regulated only by HHS, the RO must file an application with CDC's Select Agent Program (Address: Centers for Disease Control and Prevention, Select Agent Program, 1600 Clifton Rd NE, Mailstop E-79, Atlanta, Georgia 30333). A listing of HHS select biological agents and toxins is available at http://www.cdc.gov/od/sap. Help with questions is available by calling 404-498-2255.

- For agents regulated only by USDA, the RO must file an application with APHIS (Address: Animal and Plant Health Inspection Service, Agriculture Select Agent Program, 4700 River Road, Unit 2, Mailstop 22, Cub 1A07, Riverdale, MD, 20737). A listing of USDA animal agents and toxins is available at http://www.aphis.usda.gov/vs/ncie/bta.html. The list of plant agents and toxins is available at http://www.aphis.usda.gov/ppq/permits. Help with questions is available by calling 301-734-5960.

46. What action do I take to expedite a security risk assessment?

Please see 42 CFR 73.8(g):

> "The HHS Secretary will request the Attorney General to expedite the review process for an individual and will take action to expedite the HHS Secretary's review process for an individual upon a showing of good cause (*e.g.*, public health or agricultural emergencies, national security, impending expiration of a research grant, a short-term visit by a prominent researcher). To apply for an expedited review, an entity must submit a request in writing in accordance with § 73.21 to the HHS Secretary establishing the need for such action. The HHS Secretary will provide a written decision granting the request, in whole or in part, or denying the request."

The entity must show good cause for the expedite request. As the examples of good cause indicate, a request to expedite the security risk assessment process is not intended to be used as part of an entity's routine hiring process.

Prior to the request for expedite, the entity should submit:

- A completed 4B and all other appropriate parts of the CDC FORM 0.1319 / APHIS FORM 2044 - Application for Laboratory Registration for Possession, Use, and Transfer of Select Biological Agents and Toxins. The Select Agent Program will issue the DOJ unique identifier to the RO, who should follow the process of applying for the security risk assessment (SRA) (see question 20). To avoid delays, it is recommended that the RO check that the Table 4B information is the same as that supplied on the individual(s) Form FD-961.
- The RO should confirm that the individual(s) for which the expedite is requested have already submitted the form and fingerprints to CJIS prior to submitting the request for expediting SRA's. Failure to submit form and fingerprints prior to submission of the request for expedite may result in denial of the request.

47. Is there anything I can do to avoid delays in the security risk assessment results?

Common errors may delay the security risk assessment process. Please pay careful attention to:

- The name (including the middle initial), the date of birth and address, (including zip code) for individuals listed on the Table 4B (CDC Form 0.1319). This information should be identical to that given on the Form FD-961 submitted to CJIS for each individual.
- Typographical errors regarding date of birth are very common.
- Information for staff, agent, principal investigator, or room that do not agree with corresponding information on file for principal investigator, agents and rooms

already registered will delay the processing of amendments or update to an application. These errors must be resolved prior to the release of a SRA approval letter by the CDC Select Agent Program.